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C-reactive protein as a predictor of posttraumatic stress induced by acute myocardial infarction

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Abstract: BACKGROUND: Acute coronary syndrome (ACS) may cause clinically relevant posttraumatic stress disorder symptoms (PTSS). An inflammatory state might be one mechanism linking PTSS with poor prognosis after ACS. We tested the hypothesis that a change in C-reactive protein (CRP) between hospital admission and 3-month follow-up is an independent predictor of ACS-triggered PTSS. **METHODS:** We assessed 183 patients (median age 59 years; 84% men) with verified myocardial infarction (MI) within 48 h of an acute coronary intervention and three months post-MI for self-rated PTSS. 14 (7.7%) patients fulfilled definition criteria for PTSS caseness. CRP values were categorized according to the predicted risk of cardiovascular disease (CVD) at hospital admission (acute inflammatory response): 0 to <5 mg/L, 5 to <10 mg/L, 10 to <20 mg/L, and ≥ 20 mg/L; and at 3-month follow-up (low-grade inflammation): 0 to <1 mg/L, 1 to <3 mg/L, and ≥ 3 mg/L. Additionally, in a subsample of 84 patients with CRP levels below 20 mg/L at admission, CRP values were log-transformed. **RESULTS:** After adjustment for covariates, less of a reduction or an increase of log CRP values between admission and 3-month follow-up predicted PTSS caseness (OR 6.25, 95% CI 1.25, 31.38), and continuous PTSS (unstandardized B = 0.21, 95% CI 0.07, 4.19; p = 0.043). Less reduction in CRP risk categories predicted both PTSS caseness (OR 4.14, 95% CI 1.89, 9.06) and continuous PTSS (B = 1.80, 95% CI 1.09, 2.51; p < 0.001). **CONCLUSIONS:** Persistently heightened inflammation seems to be predictive for the development of PTSS three months after ACS, so interventions to lower inflammation might be warranted.

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Short title: CRP predicting posttraumatic stress after acute MI

ABSTRACT

Background: Acute coronary syndrome (ACS) may cause clinically relevant posttraumatic stress disorder symptoms (PTSS). An inflammatory state might be one mechanism linking PTSS with poor prognosis after ACS. We tested the hypothesis that a change in C-reactive protein (CRP) between hospital admission and 3-month follow-up is an independent predictor of ACS-triggered PTSS.

Methods: We assessed 183 patients (median age 59 years; 84% men) with verified myocardial infarction (MI) within 48 h of an acute coronary intervention and three months post-MI for self-rated PTSS. 14 (7.7%) patients fulfilled definition criteria for PTSS caseness. CRP values were categorized according to the predicted risk of cardiovascular disease (CVD) at hospital admission (acute inflammatory response): 0 to <5 mg/L, 5 to <10 mg/L, 10 to <20 mg/L, and ≥ 20 mg/L; and at 3-month follow-up (low-grade inflammation): 0 to <1 mg/L, 1 to <3 mg/L, and ≥ 3 mg/L. Additionally, in a subsample of 84 patients with CRP levels below 20 mg/L at admission, CRP values were log-transformed.

Results: After adjustment for covariates, less of a reduction or an increase of log CRP values between admission and 3-month follow-up predicted PTSS caseness (OR 6.25, 95% CI 1.25, 31.38), and continuous PTSS (unstandardized B =0.21, 95% CI 0.07, 4.19; p=.043). Less reduction in CRP risk categories predicted both PTSS caseness (OR 4.14, 95% CI 1.89, 9.06) and continuous PTSS (B=1.80, 95% CI 1.09, 2.51; p<0.001).

Conclusions: Persistently heightened inflammation seems to be predictive for the development of PTSS three months after ACS, so interventions to lower inflammation might be warranted.

Keywords: Cardiovascular disease; inflammation; psychobiology; risk factor; trauma stress

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a mental disorder that potentially develops after the acute phase of a traumatic event and, according to the DSM-IV (Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994). It is characterized by symptoms of re-experiencing, avoidance and hyperarousal. In the aftermath of acute coronary syndrome (ACS), such as myocardial infarction (MI), PTSD and clinically relevant PTSD symptoms (PTSS) develop in 4% and 12%, respectively ¹.

PTSD/PTSS are associated with adverse cardiovascular outcome ²⁻⁴. The literature suggests that PTSD may contribute to a pro-inflammatory state ⁵, but also that elevated levels of the inflammatory marker C-reactive protein (CRP) could be a risk factor for developing PTSD. In war zone veterans, higher baseline CRP levels before deployment predicted a higher risk of PTSS 3 months after deployment, adjusting for baseline PTSS, trauma exposure and other relevant covariates. ⁶ More specifically, PTSD may be linked via a pro-inflammatory state, characterized by elevated levels of CRP, ^{7,8} to the development of coronary heart disease (CHD) ^{9,10}. Whether trajectories in CRP from levels during the acute phase reaction of MI (i.e. acute inflammatory response) to levels in stable CHD (i.e., chronic low-grade inflammation) are predictive of MI-triggered PTSS has not previously been investigated.

We recently showed a correlation between elevated CRP levels and MI-triggered acute stress disorder (ASD) symptoms assessed within 48 h of admission for MI ¹¹. The latter may precede PTSD ¹² and are also prognostic for long-term mortality in patients with ACS ¹³. Specifically, independent of demographics, health behaviors, cardiac-related variables and psychosocial factors, we found that ASD symptoms were associated with CRP levels of 20 mg/L or higher, reflecting high risk of poor cardiovascular outcome ¹¹.

Therefore, from a perspective of personalized medicine aimed at providing optimal risk-guided individual cardiovascular prevention therapy ¹⁴, we firstly investigated whether changes in CRP levels between the acute phase of MI and stable CHD at follow-up are predictive of MI-triggered PTSS caseness and continuous PTSS. Secondly, to evaluate a categorical model for a rapid assessment of clinical risk in an emergency situation, we classified patients with ACS into categories of increased cardiovascular risk according to CRP levels. These were measured twice, once in the hospital during the acute phase of MI, and once three months later, when CHD was stable and PTSS were also assessed. Based on data from prospective cohort studies, categories of high-sensitivity (hs-)CRP levels ¹⁵ add prognostic information above and beyond the Framingham CHD risk score of incident cardiovascular events ¹⁶.

The primary hypothesis of our study was that less of a decrease in continuous CRP measures between the acute phase of MI and 3-month follow-up predicts MI-triggered PTSS caseness and also higher levels of continuous PTSS, independent of previously identified risk factors, including ASD symptoms ¹¹. Our second hypothesis was that this relation would equally hold across CRP-defined cardiovascular risk categories. We hypothesized that the association between CRP levels and PTSS caseness/PTSS would be independent of ASD symptoms, while also controlling for demographic factors, health behaviors, cardiac-related variables and psychosocial characteristics.

MATERIALS AND METHODS

Patients and study design

Between January 2013 and September 2015, the Myocardial Infarction-Stress Prevention Intervention (MI-SPRINT) study recruited a sample of 190 eligible patients undergoing acute coronary care intervention due to verified acute ST-elevation MI (STEMI) or non-STEMI at the Bern University Hospital (“Inselspital”). MI-SPRINT was a randomized controlled trial which evaluated the effect of early psychological counseling on the development of PTSS at 3-month follow-up¹⁷. As previously shown¹⁸, stress counseling was more effective to reduce self-rated PTSS than trauma-focused counseling, so we considered the type of counseling as a control variable in the present study. Data reported here are from the 183 patients who were alive when the 3-month follow-up assessment was performed.

Patients were informed and gave signed consent to the study which was approved by the ethics committee of the State of Bern, Switzerland (KEK-Nr. 170/12). Included were participants 18 years or older with a need for counseling due to a substantial level of acute distress perceived during MI (i.e., they scored with at least 5 for chest pain and for fear of dying and/or helplessness on a numeric rating scale from 0-10)¹⁸. After having reached stable hemodynamic conditions, all patients underwent a structured clinical interview during which a medical history and information on health behaviors were obtained. Psychological symptom severity was collected by self-report. Fasting venous blood samples for the assessment of CRP were drawn the next morning (note that for logistical reasons, blood was collected at another time of the day and non-fasting in less than 10% of cases). At 3-month

follow-up all patients were assessed in terms of self-rated PTSS, plasma CRP levels, participation in cardiac rehabilitation, and medications.

Exclusion criteria were emergency coronary artery bypass grafting, any serious comorbid disease likely to cause death within one year, cognitive impairment, current severe depression (according to the cardiologist's clinical judgement), suicidal ideations in the last two weeks, insufficient knowledge of German language, and participation in another randomized controlled trial.

Measures

Posttraumatic stress disorder symptoms: Self-rated PTSS were assessed with the German version of the 17-item posttraumatic diagnostic scale (PDS), whereby replacing the term "event" with the term "heart attack". Each item is rated on a 4-point Likert scale as to how frequent a particular symptom had occurred during the past month (0 = "not at all," 3 = "often"). To rate PTSS severity at three months post-MI, we calculated a sum score (range 0-51) and we also applied a cut-off of 15+ to identify cases at "high risk" for DSM-IV subsyndromal plus syndromal PTSD combined¹⁹. For participants with elevated PTSS meeting the 15+ cut-off score on the PDS, we used the term "PTSS caseness". Internal consistency was previously considered to be good in a cardiac sample (Cronbach α sum score = .91)² as well as in the current sample (Cronbach α sum score = .89).

Acute stress disorder symptoms: The German version of the ASD-Scale (ASDS) was used to assess the prevalence of psychiatric symptoms of MI-induced acute distress²⁰. The ASDS comprises subscales of dissociation (5 items), re-experiencing (4 items), avoidance (4 items) and arousal (6 items). Each item is scored on a 5-point Likert scale, yielding a ASD sum score between 0 and 95²¹. Case definition criteria for ASD are met with a sum score of 28+.

Further covariates: Trained study staff assessed suicidal thoughts (yes/no) in the last two weeks with item 9 of the patient health questionnaire-9²², with immediate referral for psychiatric evaluation to follow in case of active plans for attempting suicide²³. Perceived social support was assessed with the Enhancing Recovery in CHD Patients Social Support Inventory, comprising dimensions of emotional, structural, and instrumental support, rated with 6 items on a Likert scale from 0 ("none of the time") to 4 ("all the time") (Mitchell et al. 2003). Socioeconomic status (SES) was defined with reference to high, medium, or low level of education²⁵. Participants further disclosed their weight and height for the calculation of the BMI, smoking habits (current, former or never smokers), level of physical activity ("that makes you sweat") in terms of the number of times in an average week, and consumption of alcoholic beverages. According to the J-shaped risk between alcohol intake and CVD risk²⁶, we categorized participants on a scale from 0-2 as moderate drinkers, non-drinkers, and heavy drinkers (>21 drinks/week for men, >14 drinks/week for women). CVD-related measures were STEMI vs. non-STEMI, left ventricular ejection fraction (LVEF), peak troponin T levels, white blood cell count, and the Global Registry of Acute Coronary Events (GRACE) risk score, which combines eight variables for an estimate of the risk of post-discharge death and recurrent MI after ACS²⁷. Prescribed antidepressants were also noted.

C-reactive protein: CRP was measured in lithium-heparin plasma with an immunoturbidimetric assay (C-Reactive Protein Gen.3, measuring range 0.3-350 mg/L) using the COBAS 8000 c702 module from Roche Diagnostics. The assay was performed according to the manufacturer's instructions at the Central Laboratory for Clinical chemistry - CoreLab, Bern University Hospital, Switzerland. Note that for clinical routine, the CoreLab provides CRP values of 20 mg/L and higher as "CRP \geq 20 mg/L", but does not indicate the precise concentration above this level. To evaluate a categorical model for a rapid assessment of clinical risk in an emergency situation (i.e., at hospital admission), circulating levels of CRP

assessed in the acute phase of MI were categorized according to the prognostic risk of hs-CRP levels for incident cardiovascular events and classified as follows: 0 to <5 mg/L =1, 5 to <10 mg/L =2, 10 to <20 mg/L =3, and ≥ 20 mg/L =4¹⁶. At follow-up, the cut-points to classify our patients with stable CHD in terms of an increased risk of adverse cardiovascular outcome were <1.0 mg/L =1, 1-3 mg/L =2, and >3 mg/L =3, corresponding to low, average and high risk, respectively. These cut-offs correspond to approximate tertiles of hs-CRP in the adult population and reflect an increasing risk of incident CVD and poor prognosis in stable CHD¹⁵. The change of CRP risk categories (Δ cat-CRP) over time was defined as classified risk category at follow-up minus classified risk category at admission. This means that patients with a Δ cat-CRP of “-3” have the greatest decrease in CVD risk over time, since they shifted from the highest risk category at admission to the lowest one at follow-up.

Statistical analyses

Data were analyzed using SPSS 24.0 for Windows (SPSS Inc., Chicago, IL) with level of significance at $p < 0.05$. Missing values of variables of interest were replaced with the expectation maximization algorithm to make use of all the available information from the total sample of 183 MI survivors. Little’s missing completely at random tests revealed no significant patterns in the data before performing imputations (i.e., CRP measures were missing at random). Information on ASDS and PDS scores was missing in 36 and 35 cases each. The GRACE risk score could not be computed for 18 patients; 43 cases missed social support indications. CRP was not measured in 17 cases at admission and in 63 cases at follow-up due to technical and logistic reasons. Four or less values were missing for the other measures. CRP levels below 20mg/L were not normally distributed and thus log-transformed.

Binary and linear regression analyses were applied. Firstly, we investigated the association of the change in continuous CRP levels from admission to 3 months follow-up

(Δ -logCRP) with PTSS caseness and continuous PTSS, respectively, in the 84 MI survivors with CRP measurements below 20mg/L at both assessments. To be consistent with our previous publication ¹¹, both analyses controlled for gender, education, BMI, LVEF, white blood cell count, and ASD symptoms (sum score) as covariates in the regression models. The result of this calculation equals the percent change in PDS scores associated with each 1-point increase in log-transformed CRP.

Secondly, in all 183 MI survivors, we investigated the association of the change in categorical CRP levels from admission to follow-up with PTSS caseness and continuous PTSS, respectively. In these analyses, we controlled for gender, age, education, BMI, smoking status, alcohol intake, physical activity, STEMI, GRACE risk score, LVEF, troponin T, white blood cell count, social support, ASD symptoms, antidepressants, and the type of counseling intervention. The latter was considered as it previously showed an effect on the PDS sum score at 3 months follow-up ¹⁸.

The above mentioned demographic factors, health behaviors, cardiac-related variables and psychosocial factors were taken into account as covariates a priori, as they might potentially confound associations with PTSS based on the literature. To protect against model overfitting, we allowed a maximum of seven and 17 predictor variables in the models with continuous CRP and categorical CRP measures, respectively. Inspection of variance inflation factors indicated no concern for multicollinearity.

RESULTS

Patient characteristics

The characteristics of the 183 study participants with a median age of 59 years (range 18-88) are shown in Table 1. The PDS sum score ranged between 0 and 29 (median 3.0) with 14 (7.7%) patients reaching case definition criteria for PTSS. The latter had received more

trauma-focused interventions (as published elsewhere ¹⁸), and they also had more ASD symptoms and reported more frequent use of antidepressants (Table 1). The median of the GRACE was 105 (range 52-214) corresponding to a median risk of 5% (range 3-9) for post-discharge death in the next six months. The ASD symptom score ranged from 0 to 45 (median 15.0) and 18 (9.8%) patients met case definition criteria for ASD.

Association of continuous CRP changes with PTSS caseness and continuous PTSS

In the 84 MI survivors with CRP measurements below 20mg/L at both assessments, eight patients had PDS scores above the cut-off for PTSS caseness. The binary logistic regression analysis showed that less of a reduction or an increase of log CRP values between admission and 3-month follow-up predicted PTSS caseness (OR 6.25, 95% CI 1.25, 31.38; $p=.026$). This was independent from the predictive value of ASD symptoms (OR 1.17, 95% CI 1.05, 1.30; $p<.005$); the other covariates in the model, which were gender, education, BMI, LVEF, and white blood cell count, were not significantly associated with PTSS caseness. Figure 1, depicts the distribution of log CRP levels between patients with PTSS caseness ($n=8$) and those without ($n=76$) at admission and at follow-up. The two groups did not significantly differ in their CRP levels at admission ($p=0.10$) and at follow-up ($p=0.22$).

There was a significant associations between the change in continuous CRP measures from admission to follow-up and continuously scaled PTSS at follow-up (unstandardized $B = 0.21$, 95% CI 0.07, 4.19; $p=.043$); this analysis also controlled for gender, education, BMI, LVEF, white blood cell count and ASD symptoms. A significant relationship emerged for ASD symptoms ($B=0.34$, 95% CI 0.22, 0.45; $p<.001$). The other covariates in the model were not significantly associated with continuous PTSS.

Association of categorical CRP changes with PTSS caseness and continuous PTSS

In the total sample of the 183 MI survivors, CRP levels at admission were categorized as 1 for n=34; 2 for n=20; 3 for n=30; and 4 for n=82 patients, missing n=37. At 3-month follow-up, CRP levels were categorized as 1 for n=63, 2 for n=41; and 3 for n=16 patients, missing n=63. After imputation for missing data, Δ cat-CRP was -3 for n=20; -2 for n=59; -1 for n=49; 0 for n=42; 1 for n=11; and 2 for n=2 patients.

Table 2 shows the fully adjusted binary regression model for the association between Δ cat-CRP and PTSS caseness in the 183 patients. A patient with a transition from a lower CRP risk category at admission to a higher CRP risk category at 3-month follow-up had a significantly greater risk of developing PTSS caseness and vice versa, independent of all covariates in the model. In addition to ASD symptoms, lower level of education was also significantly predictive of PTSS caseness at follow-up.

In the linear regression analysis, Δ cat-CRP was also an independent predictor of continuous PTSS ($B=1.80$, 95% CI 1.09, 2.51; $p<0.001$), indicating that a greater decrease in CRP risk scores over time predicted less PTSS at follow-up. Covariates were the same as specified in the model for PTSS caseness above. Of covariates, independent relationships with continuous PTSS emerged for ASD symptoms ($B=0.35$, 95% CI 0.27, 0.43; $p<0.001$), lower level of education ($B=-3.05$, 95% CI -4.43, -1.66; $p<0.001$), LVEF ($B=-.08$, 95% CI -.15, -.00; $p=.041$), use of antidepressants ($B=3.19$, 95% CI 0.44, 5.94; $p=.023$) and stress- vs. trauma-focused counseling ($B=-1.98$; 95% CI -3.34, -0.63; $p=.004$).

DISCUSSION

In patients with ACS, this study examined the association of changes over time in inflammation and MI-induced PTSS assessed three months after the cardiac event. We found circulating CRP concentrations at levels of higher prognostic risk of CVD between hospital admission and 3 months post-MI to be predictive of PTSS caseness and also of greater levels

of continuous PTSS. Specifically, continuous and categorical measures of CRP were both predictive of PTSS caseness and continuous PTSS, and potentially modulating effects of demographics, health behaviors, cardiac-related variables, and psychosocial factors were taken into account. Therefore, the predictive value of inflammation for PTSS seems robust.

In agreement with a previous study ³⁰, we found that ASD symptoms assessed at admission predicted PTSS caseness and continuous PTSS independently of changes in CRP levels over time. Based on this finding and our previous finding of an association between ASD symptoms and CRP levels at hospital admission ¹¹, the acute phase response to MI could be considered as a set-off-point for PTSS onset that can be determined by a multitude of factors; these may include accumulated risk from early childhood ²⁸ transmitted via low adult SES, unhealthy behaviors, including high BMI, and impaired quality of life ²⁹.

We further found low education to be a predictor of PTSS caseness and continuous PTSS in the entire sample of our MI survivors. Although, to our knowledge, this finding seems novel in patients with ACS, lower educational level has been shown to predict PTSD ³⁰, as well as increased inflammatory markers, including CRP ³¹ in other populations. As has been published elsewhere ¹⁸, one single session of early psychological counseling regarding the general role of stress in CHD versus trauma-focused counseling resulted in less continuous PTSS; however, psychological counseling was not associated with PTSS caseness, although this could reflect an issue of low statistical power.

The initial physical reactions to such events showing increase in white blood cells, troponin T levels or presence of STEMI did not predict PTSS caseness, whereas less of a reduction or increase in continuous CRP/CRP risk categories, initial ASD symptom severity and low education did. In addition, previous antidepressant medication, indicating psychiatric vulnerability, and lower LVEF were both associated with increased continuous PTSS whereas stress counseling was associated with lower levels of continuous PTSS. This

suggests that the psychological response to the event is at least as important as the severity of the cardiac disease for the development of PTSS³². However, we are unable to rule out the possibility that elevated levels of PTSS could contribute to increased CRP levels at 3-month follow-up, for instance through heightened arousal or autonomic dysfunction.

The findings from our study may have clinical implications. The assessment of CRP levels with respect to their prognostic value of CVD risk during the acute inflammatory response and at follow-up could be used to identify patients at risk to develop clinically relevant PTSS, which in their own right may impact on cardiovascular prognosis¹. Although after the acute inflammatory response during admission, we assessed CRP and PTSS only once, i.e., three months post-MI, it might be worthwhile to examine whether a trajectory lacking a drop in risk levels of CRP over time is a biological predictor of PTSS even before 3 months post-MI. This may indicate an early need for tailored preventive interventions for individuals at risk to develop PTSS/PTSD. To substantiate such a clinical utility, future studies are needed to evaluate whether the systematic assessment of CRP could improve the evidence of primary prevention programs of PTSS/PTSD in patients with ACS³³ and whether changes in CRP are equally relevant for the outcome of other types of trauma³⁴.

Limitations: We measured CRP with a conventional immunoturbidimetric method, whereas the preferable marker for CVD risk assessment is hs-CRP, although studies show that these methods are similarly predictive of mortality in patient samples³⁵. There may be unmeasured factors impacting on change in CRP risk categories over time, such as triglycerides or blood-pressure³⁶. In addition, we considered only one marker of inflammation (CRP) and thus further research is needed to examine whether these findings generalize to other inflammation-related biomarkers⁵. Investigating the biological mechanisms of MI, ASD and the development of PTSD, future studies also need to consider the assessment of CRP polymorphisms. For instance, one study suggested that T carriers of

the rs1205 CRP polymorphism had lower CRP concentrations than C/C carriers in ACS³⁷. Since CRP polymorphisms have been associated with greater risk of PTSD/PTSS^{38,39}, variations in the CRP gene might underlie both high levels of CRP and a greater risk of PTSD in the context of ACS. Furthermore, we did not assess depression which is known to be associated with elevated CRP and PTSD, and PTSS caseness was based on a self-report inventory rather than on a diagnostic interview using the former DSM-IV perspective. The specifics of patients participating in the MI-SPRINT randomized controlled trial prevent generalization of our findings to the ACS population at large. Our patients experienced a substantial level of distress during MI, had rather low somatic and mental comorbidity, and the majority were men with a socioeconomic status above average.

To sum up, our findings demonstrate that a shift of inflammation between the acute phase of MI and stable CHD at follow-up may predict the development of clinically relevant PTSS independently of ASD symptoms and other important covariates. This study showed a correlation between changes in CRP from baseline to 3-month follow-up and PTSS at three months. Future studies considering multiple assessments of both CRP and PTSS over time are warranted to evaluate whether there are trajectories in CRP levels before patients develop PTSS/PTSD.

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